

Adverse Pregnancy Outcomes in Asthmatic Women: A Population-Based Family Design Study



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What is already known about this topic? Asthma affects a large proportion of pregnant women worldwide and is associated with adverse outcomes. Unknown and unmeasurable confounders might play a role in the association between asthma and adverse pregnancy and delivery outcomes.

What does this article add to our knowledge? We found that the association between asthma and adverse pregnancy, delivery, and perinatal outcomes remained after adjusting for genetic and environmental factors shared by siblings and cousins.

How does this study impact current management guidelines? Maternal asthma continues to be an important clinical target to diminish risks of adverse pregnancy, delivery, and perinatal outcomes.

BACKGROUND: Asthma is associated with several adverse pregnancy and perinatal outcomes. Familial factors may confound these associations.

OBJECTIVE: To examine the role of measured and unmeasured confounding by conducting a study that compared differentially exposed cousins and siblings from the same families.

METHODS: We retrieved data on adverse pregnancy outcomes, prescribed drugs, and physician-diagnosed asthma from nationwide registers for all women in Sweden with singleton births between 2001 and 2013. Logistic and linear regression estimated the association between maternal asthma and several outcomes in the whole population and within differently exposed pregnant relatives.

RESULTS: In total, 1,075,153 eligible pregnancies were included and 10.1% of the study population had asthma. We identified 475,200 cousin and 341,205 sister pregnancies. Women with asthma had increased risks for preeclampsia (adjusted odds ratio [aOR], 1.17; 95% CI, 1.13-1.21), emergency cesarean section (aOR, 1.24; 95% CI, 1.22-1.27), and having a child small for gestational age (aOR, 1.18; 95% CI, 1.12-1.23). In the conditional regression analyses, after adjustment for familial factors, the associations remained: preeclampsia in cousins (aOR, 1.16; 95% CI, 1.07-1.25) and siblings (aOR, 1.23; 95% CI, 1.08-1.38), emergency cesarean section in cousins (aOR, 1.28) and siblings (aOR, 1.21), and small for gestational age in cousins (aOR, 1.17) and siblings (aOR, 1.13).

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Abbreviations used
aOR- Adjusted odds ratio

CONCLUSIONS: Factors shared by siblings and cousins do not seem to explain the observed association between maternal asthma and adverse pregnancy outcomes. This implies that targeting the asthma disease will continue to be important in reducing risks for adverse outcomes in pregnancy. © 2017 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). (J Allergy Clin Immunol Pract 2018;6:916-22)

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Asthma is a common disease that affects a large proportion of the population; its prevalence is estimated to be 8% to 10% among women of childbearing age.^{1,2} There are substantial genetic influences on asthma in the adult population,³ and shared environmental factors, such as family size, smoking, socioeconomic status, and health management behavior, have also been shown to play a role in the development of the disease in adults.⁴⁻⁶ Previous studies have shown increased risks of several adverse pregnancy and delivery outcomes in women with asthma^{7,8} and in a large population-based study we recently found associations between asthma in pregnant women and several adverse pregnancy, delivery, and birth outcomes, regardless of the level of asthma control.⁹ However, it is not known to what extent genetic and familial environmental factors play a role for these adverse outcomes in women with asthma.

To account for some of these unmeasured possible confounders, it is possible to use a quasi-experimental design with cousin/sibling controls. This family-based design allows for adjustments for all factors shared between siblings or cousins. If such analyses show an equally strong association after these adjustments, the exposure studied (in this case maternal asthma) is a potential causal risk factor for the outcome. If the association weakens compared with that based on unrelated controls, it is likely that familial factors have confounded the observed association. A family-based design does not confirm causality, but it gives stronger support of a causal effect compared with ordinary observational studies because it is possible to adjust for some important unmeasured, unmeasurable, or unknown confounders.¹⁰⁻¹³

Our hypothesis was that maternal asthma is causally related to adverse pregnancy outcomes such as preeclampsia or eclampsia, placental abruption, delivery mode, birth weight, and gestational age. To test our hypothesis rigorously, we adjusted for measured covariates as well as unmeasured genetic and shared familial factors by conducting a register-based study, with sibling and cousin control designs, based on all women who gave birth in Sweden during the period 2001 to 2013.

METHODS

Study design and population

This population-based study was conducted using several Swedish health and population registers. The registers were linked using the unique personal identification number assigned to all permanent

residents of Sweden.¹⁴ We used the Swedish Medical Birth Register,^{15,16} covering approximately 99% of all births in Sweden, to identify all women giving birth in the years 2001 to 2013. In a second step, we linked these women to the Multi Generation Register¹⁷ to identify full sisters and full cousins. In addition, we used information from the National Patient Register, which covers all inpatient care in Sweden since 1987 and 75% of all outpatient visits from 2001,¹⁸ and the Swedish Prescribed Drug Register, which contains all prescribed drugs dispensed at pharmacies in Sweden since July 1, 2005.¹⁹ The use of a prescription for asthma medication in the Swedish Prescribed Drug Register as a proxy for asthma disease has been validated previously.²⁰

We excluded multiple gestation pregnancies because their characteristics often differ from those in singleton pregnancies, making any observed associations difficult to interpret.²¹ Permission for this study was obtained from the Regional Ethical Review board in Stockholm, Sweden (reference 2014/2037-32). In accordance with their decision, we did not obtain informed consent from participants involved in the study. All data were deidentified before analyses.

Exposure

Our exposure was maternal asthma from the age of 15 years until delivery. Information on asthma was collected from 3 different sources: the National Patient Register; the Medical Birth Register with information on pregnancy, delivery, and perinatal outcomes and diagnoses recorded at antenatal visits and delivery wards; and records of asthma medication from the Swedish Prescribed Drug Register. From the National Patient Register and the Medical Birth Register we identified asthma diagnoses (code 493 according to the *International Classification of Diseases, Ninth Revision*, and codes J45 and J46 according to the *International Classification of Diseases, Tenth Revision*). From the Medical Birth Register, we collected data on whether the mother had ever had asthma (a question asked by the midwife in early pregnancy and present as a tick-box), and from the Prescribed Drug Register, for women being pregnant from July 1, 2006, we identified all those who had asthma medication dispensed at least twice from the year before pregnancy until delivery (Anatomical Therapeutic Chemical Classification System codes R03AC, R03AK, R03BA, and R03DC).

Outcome

The outcome data (pregnancy, delivery, and perinatal complications and diagnoses) were collected from the Medical Birth Register based on the *International Classification of Diseases, Tenth Revision* codes for preeclampsia/eclampsia (O14-15) and placental abruption (O45). We also assessed the mode of delivery and several birth outcomes (birth weight and gestational age as well as small and large for gestational age²²).

Covariates

Possible confounders were selected using directed acyclic graphs²³ and collected from the Medical Birth Register (smoking [none/1-9 cigarettes/≥10 cigarettes per day], body mass index, civil status [married or cohabiting/single/other situations], and the participant's country of birth [Sweden/other Scandinavian countries/rest of the world]). All data used from the Medical Birth Register were reported at the first antenatal visit. There are data on body mass index and smoking during pregnancy as well but those data are not as reliable. Socioeconomic status, defined as the highest level of education, was extracted from the longitudinal integration database for health insurance and labor market studies (LISA by Swedish acronym)

maintained by Statistics Sweden²⁴ (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

Statistical analyses

In a first step, we assessed the prevalence of asthma and its effects on pregnancy outcomes and we performed logistic and linear regression analyses, for categorical and continuous outcome variables, respectively. We estimated the crude and adjusted odds ratios (aORs) and average difference in mean birth weight/gestational age with 95% CIs in the full cohort.⁹ In a second step, we used conditional logistic regression, conditioning on full sibling pairs (same mother and father) and cousin pairs (common grandparents) in separate analyses, and for the continuous outcomes a linear regression model with fixed effects estimator. We could then estimate associations adjusted for genetic factors (for sisters on average 50% and cousins 12.5%) and shared (familial) environment. If the statistical association is due to familial confounding, the comparison of differently exposed pairs will result in changed estimates, with a possible gradient from the full cohort, to cousins to siblings.²⁵ Some women contributed with more than 1 pregnancy, which caused dependency within clusters. Therefore, we used the sandwich estimator in the logistic and linear regression analyses for the full cohort and bootstrapping of clusters with 200 repetitions to estimate 95% CIs for the cousin and sibling analyses.

We also performed a sensitivity analysis using either only asthma diagnosis (from the National Patient Register, the Medical Birth Register) or only prescribed drugs (from the Prescribed Drug Register). Furthermore, in a sensitivity analysis, we did single-year analyses, constraining the years to either 2001 or 2013 to find out whether different years of pregnancy and birth affect the observed associations, considering the more complete asthma information from 2005 and onward.

All analyses were done using STATA 14 (StataCorp LLC, College Station, Texas).

RESULTS

In a study population of 661,956 women we identified 1,075,153 eligible pregnancies between the years 2001 and 2013. In total 321,339 women had 1 pregnancy, 277,268 had 2 pregnancies, and 63,349 women had 3 or more pregnancies. Asthma according to our definition was defined for 108,225 pregnancies (10.1%). We identified 475,200 pregnancies in full cousin pairs and 341,205 in full sister pairs during the study period; background characteristics are presented in Table 1. The number of cousins and siblings with asthma and giving birth during the study period was 48,620 (43,286 with full covariate information) and 32,905 (29,317 with full covariate information), respectively.

In the full cohort analyses, women with asthma had increased risks for both preeclampsia/eclampsia (aOR, 1.17; 95% CI, 1.13-1.21) and placental abruption (aOR, 1.27; 95% CI, 1.15-1.41). Furthermore, instrumental and cesarean deliveries were more common in women with asthma than in women without asthma; for instance, instrumental delivery (aOR, 1.09; 95% CI, 1.07-1.12) and emergency cesarean section (aOR, 1.24; 95% CI, 1.22-1.27) (Table II). Children born to women with asthma had a lower mean birth weight (47 g lower, 95% CI, 42-51 g) and the mean gestational age was 0.12 weeks lower (95% CI, 0.11-0.13). There was also an increased risk of small for gestational age (aOR, 1.18; 95% CI, 1.12-1.23) and a decreased risk of large for

gestational age (aOR, 0.92; 95% CI, 0.88-0.95) among women with asthma (Table II).

When we analyzed cousins and sisters discordant for the exposure, the estimates found in the full cohort analyses remained essentially unchanged for preeclampsia/eclampsia (aOR in cousins, 1.16; 95% CI, 1.07-1.25; aOR for siblings, 1.23; 95% CI, 1.08-1.38) and slightly attenuated for placental abruption (aOR in cousins, 1.19; 95% CI, 0.88-1.49 and aOR in siblings, 1.10; 95% CI, 0.76-1.44). Similarly, the estimates for modes of delivery also remained (eg, emergency cesarean section aOR in cousins, 1.28; 95% CI, 1.20-1.36 and aOR in siblings, 1.21; 95% CI, 1.09-1.33) (Table II).

For the association between maternal asthma and perinatal outcomes (Table II), the estimates for birth weight found in the full cohort remained for cousins (39 g lower, 95% CI, 32-46 g) and siblings (34 g lower, 95% CI, 24-44 g). For the association between maternal asthma and gestational age, the estimates found in the cohort analyses also remained in the analyses for cousin pair (0.10 weeks shorter, 95% CI, 0.07-0.12 weeks) and sibling pairs (0.06 weeks shorter, 95% CI, 0.03-0.09 weeks). In the small and large for gestational age analyses, the OR estimates for cousins and siblings were also very close to those in the full cohort, although for siblings the effect was no longer statistically significant.

The sensitivity analyses showed no apparent differences between different sources of data on asthma disease (see Table E1 in this article's Online Repository at www.jaci-inpractice.org), between years of delivery (see Table E2 in this article's Online Repository at www.jaci-inpractice.org), or previous (from age 15 years until 1 year before pregnancy) versus current (in the year before or during pregnancy) asthma (see Table E3 in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

In this population-based study of more than a million pregnancies, we found that maternal asthma is a risk factor for preeclampsia/eclampsia, placental abruption, vaginal instrumental delivery, cesarean section, lower birth weight, lower gestational age, and small for gestational age. This confirms our previous results.⁹ When the analysis was done exclusively on cousins and full siblings, the estimates for preeclampsia/eclampsia, vaginal instrumental delivery, cesarean section, lower birth weight, and gestational age remained significantly more common in women with asthma than in women without asthma, suggesting that the association between asthma and these outcomes is not confounded by common environment, shared genes, or measured covariates. The findings are consistent with a causal effect between maternal asthma and these adverse pregnancy outcomes.

Previous studies

In several previous studies on the potential risk factors of maternal asthma on placental abruption, low birth weight, prematurity, and small for gestational age,^{26,27} findings have suggested that these conditions, along with preeclampsia, share common pathophysiological mechanisms involving a defect in the physiologic transformation of the spiral arteries of the placenta²⁸—an ischaemic placental disease. Although such a condition might not necessarily be a direct effect of a respiratory disease such as asthma, it could at least be significantly worsened because of intermittent maternal hypoxia or disease-related

TABLE I. Background characteristics of study population of 1,075,153 pregnancies by asthma status*

Maternal characteristic	Asthma cohort		Asthma cousins		Asthma sisters	
	No (n = 966,928)	Yes (n = 108,225)	No (n = 426,580)	Yes (n = 48,620)	No (n = 308,300)	Yes (n = 32,905)
Age (y)						
Median age	30	30	30	30	30	30
Mean	30.3	29.8	30.2	29.7	29.9	29.6
≤19	14,985 (1.5)	2,251 (2.1)	5,179 (1.2)	842 (1.7)	4,390 (1.4)	593 (1.8)
20-24	116,614 (12.1)	16,464 (15.2)	46,827 (11.0)	7,002 (14.4)	37,774 (12.3)	4,751 (14.4)
25-29	288,938 (29.9)	33,335 (30.8)	133,783 (31.4)	15,675 (32.2)	99,162 (32.2)	10,685 (32.5)
30-34	348,707 (36.1)	35,152 (32.5)	161,354 (37.8)	16,490 (33.9)	114,046 (37.0)	11,154 (33.9)
>34	197,684 (20.4)	21,023 (19.4)	79,437 (18.6)	8,611 (17.7)	52,928 (17.2)	5,722 (17.4)
BMI						
Median	23.5	24.3	23.5	24.3	23.4	24.2
Mean	24.5	25.5	24.5	25.5	24.4	25.4
<18.5	18,894 (2.0)	2,049 (1.9)	7,824 (1.8)	868 (1.8)	6,312 (2.0)	665 (2.0)
18.5-24.9	546,803 (56.6)	54,056 (49.9)	242,483 (56.8)	24,340 (50.1)	178,397 (57.9)	16,906 (51.4)
25-29.9	211,778 (21.9)	26,995 (24.9)	93,411 (21.9)	12,167 (25.0)	65,894 (21.4)	7,954 (24.2)
≥30	96,398 (10.0)	17,114 (15.8)	42,874 (10.1)	7,729 (15.9)	29,035 (9.4)	5,020 (15.3)
Missing	93,055 (9.6)	8,011 (7.4)	39,988 (9.4)	3,516 (7.2)	28,662 (9.3)	2,360 (7.2)
Parity						
1	440,390 (45.5)	52,577 (48.6)	194,475 (45.6)	23,615 (48.6)	136,802 (44.4)	15,531 (47.2)
2-3	485,735 (50.2)	50,351 (46.5)	215,805 (50.6)	22,789 (46.9)	158,139 (51.3)	15,758 (47.9)
≥4	40,803 (4.2)	5,297 (4.9)	16,300 (3.8)	2,216 (4.6)	13,359 (4.3)	1,616 (4.9)
Sex of offspring						
Boy	497,452 (51.4)	55,591 (51.4)	219,186 (51.4)	25,076 (51.6)	158,704 (51.5)	16,993 (51.6)
Girl	469,472 (48.6)	52,634 (48.6)	207,393 (48.6)	23,544 (48.4)	149,594 (48.5)	15,912 (48.4)
Missing	4 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	2 (0.0)	0 (0.0)
Cigarettes smoked/d						
0	848,500 (87.8)	94,188 (87.0)	377,005 (88.4)	42,534 (87.5)	272,350 (88.3)	28,940 (88.0)
1-9	53,004 (5.5)	8,090 (7.5)	21,630 (5.1)	3,512 (7.2)	15,835 (5.1)	2,263 (6.9)
>9	17,141 (1.8)	3,109 (2.9)	7,025 (1.6)	1,332 (2.7)	4,787 (1.6)	833 (2.5)
Missing	48,283 (5.0)	2,838 (2.6)	20,920 (4.9)	1,242 (2.6)	15,328 (5.0)	869 (2.6)
Country of birth						
Sweden	917,410 (94.9)	104,516 (96.6)	425,207 (99.7)	48,457 (99.7)	286,770 (93.0)	31,436 (95.5)
Denmark, Norway, Finland, Iceland	5,590 (0.6)	651 (0.6)	383 (0.1)	49 (0.1)	1,636 (0.5)	205 (0.6)
Other countries	43,920 (4.5)	3,058 (2.8)	990 (0.2)	114 (0.2)	19,889 (6.5)	1,264 (3.8)
Missing	8 (0.0)	0 (0.0)	425,207 (99.7)	48,457 (99.7)	5 (0.0)	0 (0.0)
Cohabitation/marital status						
Living with baby's father, married	338,651 (35.0)	35,676 (33.0)	142,343 (33.4)	15,654 (32.2)	115,235 (37.4)	11,461 (34.8)
Living with baby's father, unmarried	519,880 (53.8)	60,334 (55.7)	239,979 (56.3)	27,846 (57.3)	160,480 (52.1)	18,008 (54.7)
Not living with baby's father	45,127 (4.7)	7,069 (6.5)	17,257 (4.0)	2,915 (6.0)	13,040 (4.2)	1,948 (5.9)
Missing	63,270 (6.5)	5,146 (4.8)	27,001 (6.3)	2,205 (4.5)	19,545 (6.3)	1,488 (4.5)
Mother's education level						
≤9 y	80,629 (8.3)	12,291 (11.4)	30,626 (7.2)	5,143 (10.6)	25,945 (8.4)	3,552 (10.8)
10-12 y	408,161 (42.2)	46,558 (43.0)	179,739 (42.1)	20,824 (42.8)	126,944 (41.2)	13,786 (41.9)
13-14 y	123,968 (12.8)	13,010 (12.0)	53,879 (12.6)	5,731 (11.8)	37,538 (12.2)	3,903 (11.9)
≥15 y	333,510 (34.5)	33,654 (31.1)	154,415 (36.2)	15,801 (32.5)	111,596 (36.2)	10,906 (33.1)
Missing	20,660 (2.1)	2,712 (2.5)	7,921 (1.9)	1,121 (2.3)	6,277 (2.0)	758 (2.3)

BMI, Body mass index.

Values are n (%).

*Asthma recorded in the Swedish Medical Birth Register, asthma diagnosis in the Swedish National Patient Register, and/or asthma medication dispensed at least twice from the year before pregnancy until delivery according to the Swedish Prescribed Drug Register.

TABLE II. The association between asthma* and perinatal characteristics: Crude and adjusted linear and logistic regression cohort analysis and conditional linear and logistic regression for cousins and full sisters

Characteristic	n (%)		Crude OR (95% CI)	Adjusted‡ OR (95% CI)		
	Total population (N = 1,075,153)	Asthma: Yes (n = 108,225)	All population logistic regression	All population logistic regression (n = 96,041)	Cousin population conditional logistic regression (n = 43,286)	Sibling population conditional logistic regression (n = 29,317)
Pregnancy characteristic						
Preeclampsia or eclampsia	43,884 (4.1)	5,500 (5.1)	1.30 (1.26 to 1.33)	1.17 (1.13 to 1.21)	1.16 (1.07 to 1.25)	1.23 (1.08 to 1.38)
Placental abruption	3,962 (0.4)	491 (0.5)	1.27 (1.15 to 1.39)	1.27 (1.15 to 1.41)	1.19 (0.88 to 1.49)	1.10 (0.76 to 1.44)
Labor characteristic						
Mode of delivery						
Vaginal noninstrumental delivery	817,388 (76.0)	78,538 (72.6)	Reference	Reference	Reference	Reference
Elective CS (before start of labor)	68,197 (6.3)	8,320 (7.7)	1.31 (1.27 to 1.34)	1.32 (1.28 to 1.36)	1.36 (1.26 to 1.46)	1.25 (1.11 to 1.39)
Vaginal instrumental delivery	80,094 (7.4)	8,262 (7.6)	1.08 (1.06 to 1.11)	1.09 (1.07 to 1.12)	1.12 (1.06 to 1.19)	1.13 (1.02 to 1.23)
Emergency CS before or after start of labor	98,796 (9.2)	11,986 (11.1)	1.30 (1.27 to 1.33)	1.24 (1.22 to 1.27)	1.28 (1.20 to 1.36)	1.21 (1.09 to 1.33)
Missing	10,678 (1.0)	1,119 (1.0)				
Birth outcome and postpartum						
Birth weight (g)						
Mean	3,567	3,537	−34 (−38 to −30)‡	−47 (−51 to −42)‡	−39 (−46 to −32)‡	−34 (−44 to −24)‡
Missing	2,326 (0.2)	237 (0.2)				
Gestational age (wk)						
Mean	39.4	39.3	−0.11 (−0.13 to −0.10)‡	−0.12 (−0.13 to −0.11)‡	−0.10 (−0.12 to −0.07)‡	−0.06 (−0.09 to −0.03)‡
Missing	472 (0.0)	20 (0.0)				
Small for gestational age	22,112 (2.1)	2,590 (2.4)	1.19 (1.14 to 1.24)	1.18 (1.12 to 1.23)	1.17 (1.05 to 1.30)	1.13 (0.96 to 1.30)
Missing	2,799 (0.3)	258 (0.2)				
Large for gestational age	41,244 (3.8)	4,294 (4.0)	1.04 (1.00 to 1.08)	0.92 (0.88 to 0.95)	0.88 (0.81 to 0.95)	0.91 (0.80 to 1.01)
Missing	2,799 (0.3)	258 (0.2)				

BMI, Body mass index; CS, cesarean section.

*Asthma recorded in the Swedish Medical Birth Register, asthma diagnosis in the Swedish National Patient Register, and/or asthma medication dispensed at least twice from the year before pregnancy until delivery according to the Swedish Prescribed Drug Register.

‡Adjusted for age, BMI, parity, smoking at antenatal care admission, country of birth, cohabitation/marital status, and level of education.

‡P < .01.

inflammation. In our study, the association between maternal asthma and preeclampsia was not confounded by common environment or shared genetic factors. This supports the notion of a causal link between asthma (or some condition covarying with or caused by asthma) and preeclampsia.

For placental abruption, however, the positive association with maternal asthma was attenuated in comparisons of cousins and siblings discordant for asthma exposure. This implies that the associations with maternal asthma may be confounded by factors shared within families, such as genetic predisposition,^{29,30} health management behavior, and exposure to environmental agents. However, placental abruption may have other causes, not likely to be shared within families, such as abdominal trauma during pregnancy, chorioamnionitis, and previous cesarean section.³¹ Concerning the outcome small for gestational age, the estimates for first cousins (same maternal or paternal grandparents and on average 12.5% shared genes) fall between those for full siblings (same parents and on average 50% shared genes) and those for unrelated nonexposed individuals. This would suggest confounding from familial factors. However, the estimates differences are very small with overlapping CIs.

For the outcomes associated with asthma disease and seemingly not confounded by familial factors, there might be residual confounding by factors that cause both asthma and the outcomes studied, but not shared by siblings or cousins. Inflammatory pathways might be one of those factors, for instance, seen in the known covariation between asthma and allergies.³²

Strengths and limitations

The large study population with 1,075,153 singleton pregnancies, including 475,200 cousin pregnancies and 341,205 sister pregnancies, is a major strength of this study. The comparisons enabled us to take unmeasured familial factors into account by using cousin and sibling controls. Furthermore, both exposure (asthma) and outcomes have been validated^{15,20} and collected prospectively and independently, thus eliminating the risk of recall bias. The abundance of data and the size of the population also made it possible for us to adjust for several known confounders, such as socioeconomic status and smoking. Because it is a population-based study, it is also generalizable to other populations.

There are also some limitations to the study design. First, being a register-based study there were no data on indications for different mode of deliveries, allowing us only to speculate on the choices. Second, although cousin and sibling designs allow us to adjust for unmeasured confounding, this approach has limitations (described by Frisell et al³³) that are important to take into consideration, such as measurement errors regarding the exposure, or confounders shared to a lower extent within families. However, unmeasured confounding is unlikely to be a problem because we collected our exposure data from several independent sources, and subanalyses using the different sources alone produce similar estimates. Moreover, the variable for exposure was the same in each set of analyses and the acquired estimates were indeed not lowered for all studied outcomes in the family comparison. Also, confounders shared to a lower extent within families would, if being responsible for our observed results, be factors affecting placental abruption, birth weight, gestational age, and small for gestational age, but not preeclampsia or mode of delivery, which is unlikely. Third, in this study, because the only informative participants in the family-based analyses are those discordant for asthma and the outcomes, there is a drop in statistical power and we cannot rule

out that this is the reason for the lack of statistically significant results concerning placental abruption and small for gestational age.

The drop in power also limits us in studying subpopulations with different asthma severity. In our previous study, however, we did not see any clear trend in more adverse outcomes in controlled versus uncontrolled asthma.⁹ Finally, because this is an observational study, it is not possible to determine causation.

CONCLUSION AND IMPLICATIONS

To our knowledge, this is the first study on the effect of maternal asthma on pregnancy and delivery outcomes that uses a cousin and sibling control approach. We have shown that the associations between asthma and the adverse outcomes preeclampsia/eclampsia, instrumental delivery, cesarean section, birth weight, and gestational age do not seem to be confounded by genetic or environmental factors shared by first cousins or full siblings. By reducing familial confounding we have been able to show that familial (genetic and environmental) factors shared by cousins and siblings do not seem to explain the observed association between maternal asthma and adverse pregnancy outcomes. This implies that targeting the asthma disease will continue to be important in reducing risks for adverse outcomes in pregnancy. Further research should confirm our findings in other populations representing genetic and environmental heterogeneity as well as explore how to best monitor and individualize treatment during pregnancy in women with varying asthma phenotypes and severity.

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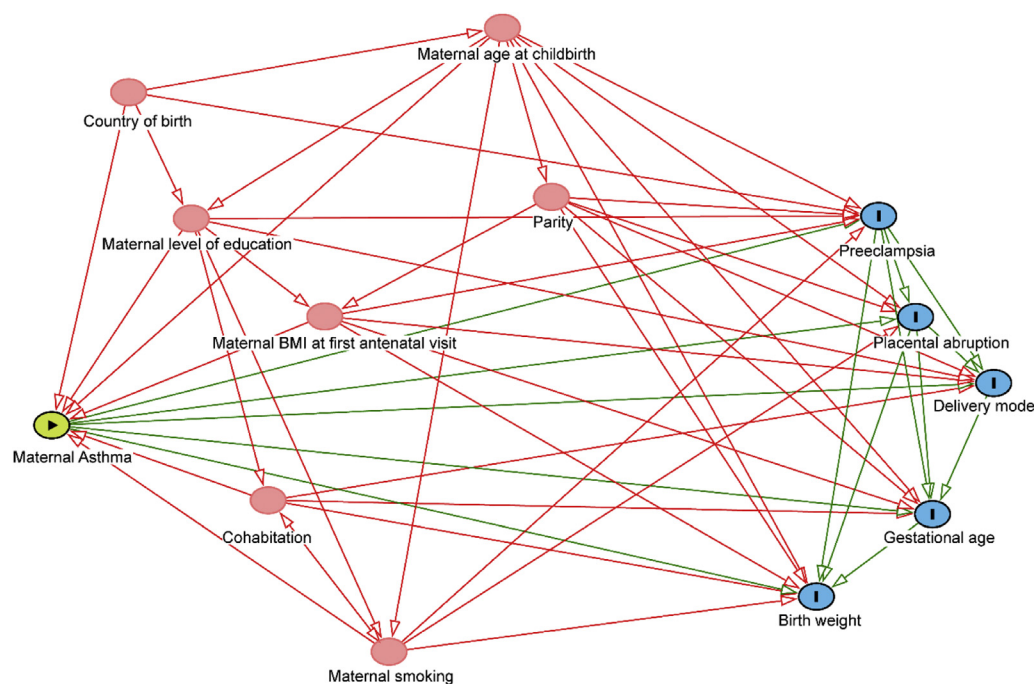


FIGURE E1. Directed acyclic graph used to select covariates for model adjustment developed using Dagitty.^{E1} The use of directed acyclic graphs is a powerful way of identifying variables that are necessary to obtain unconfounded estimates. The graphs are also helpful in determining pathways otherwise foreseen.^{E2} In the image, the covariate represented by a yellow circle with triangle shows the exposure and the blue circles with an "I" show the outcomes. The pink circles show covariates that are causally related to both the exposure and the outcome, which means they are possible confounders.

TABLE E1. The association between asthma and perinatal characteristics: Crude and adjusted logistic regression cohort analysis for total population*

					Adjusted† OR (95% CI)			
	MBR Asthma (n = 55,556 [8.1%])	NPR Ever Asthma (n = 20,509 [3.0%])	NPR During asthma (n = 4,841 [0.7%])	PDR Asthma (n = 36,883 [5.4%])	MBR All population logistic regression (n = 51,136 [8.5%])	NPR Ever all population logistic regression (n = 17,979 [3.0%])	NPR During all population logistic regression (n = 4,218 [0.7%])	PDR All population logistic regression (n = 32,548 [5.4%])
Characteristic								
Pregnancy characteristic								
Preeclampsia or eclampsia	2,835 (5.1)	1,145 (5.6)	319 (6.6)	2,104 (5.7)	1.13 (1.08 to 1.18)	1.26 (1.17 to 1.35)	1.44 (1.26 to 1.63)	1.26 (1.20 to 1.33)
Placental abruption	239 (0.4)	113 (0.6)	36 (0.7)	164 (0.4)	1.27 (1.10 to 1.47)	1.52 (1.23 to 1.88)	2.12 (1.48 to 3.03)	1.27 (1.07 to 1.51)
Labor characteristic								
Mode of delivery								
Vaginal noninstrumental delivery	40,555 (73.0)	14,676 (71.6)	3,323 (68.6)	25,811 (70.0)	Reference	Reference	Reference	Reference
Elective CS (before start of labor)	4,231 (7.6)	1,779 (8.7)	467 (9.6)	3,365 (9.1)	1.23 (1.18 to 1.28)	1.44 (1.35 to 1.52)	1.59 (1.43 to 1.78)	1.40 (1.35 to 1.47)
Vaginal instrumental delivery	4,356 (7.8)	1,477 (7.2)	359 (7.4)	2,933 (8.0)	1.12 (1.08 to 1.16)	1.07 (1.01 to 1.13)	1.17 (1.04 to 1.31)	1.20 (1.15 to 1.26)
Emergency CS before or after start of labor	6,097 (11.0)	2,444 (11.9)	653 (13.5)	4,539 (12.3)	1.19 (1.15 to 1.22)	1.31 (1.24 to 1.37)	1.48 (1.34 to 1.62)	1.33 (1.28 to 1.38)
Missing	317 (0.6)	133 (0.6)	39 (0.8)	235 (0.6)				
Birth outcome and postpartum								
Birth weight (g)								
Mean	3,540	3,503	3,479	3,509	−36 (−41 to −30)‡	−64 (−73 to −55)‡	−91 (−108 to −73)‡	−72 (−79 to −65)‡
Missing	87 (0.2)	43 (0.2)	13 (0.3)	76 (0.2)				
Gestational age (wk)								
Mean	39.3	39.2	39.1	39.2	−0.06 (−0.08 to −0.05)‡	−0.19 (−0.22 to −0.16)‡	−0.21 (−0.28 to −0.15)‡	−0.15 (−0.17 to −0.12)‡
Missing	9 (0.0)	4 (0.0)	0 (0.0)	0 (0.0)				
Small for gestational age								
Yes	1,302 (2.3)	538 (2.6)	154 (3.2)	1,023 (2.8)	1.18 (1.11 to 1.25)	1.26 (1.14 to 1.38)	1.49 (1.25 to 1.78)	1.43 (1.34 to 1.54)
Missing	98 (0.2)	48 (0.2)	14 (0.3)	77 (0.2)				

Large for gestational age								
Yes	2,064 (3.7)	819 (4.0)	175 (3.6)	1,410 (3.8)	0.90 (0.85 to 0.94)	0.95 (0.87 to 1.03)	0.81 (0.68 to 0.96)	0.87 (0.82 to 0.93)
Missing	98 (0.2)	48 (0.2)	14 (0.3)	77 (0.2)				

BMI, Body mass index; CS, cesarean section.
*Exposure is asthma from Swedish Medical Birth Register, Swedish National Patient Register, and Prescribed Drugs Register, respectively (years 2006-2013).
†Adjusted for age, BMI, parity, smoking at antenatal care admission, country of birth, cohabitation/marital status, and level of education.
‡*P* < .001.

TABLE E2. The association between asthma* and perinatal characteristics: Crude and adjusted logistic regression cohort analysis for total population for the years 2001 and 2013, respectively

Characteristic			2001 All population logistic regression		2013 All population logistic regression	
	2001 Asthma (n[%])*	2013 Asthma (n[%])*	Crude OR (95% CI), asthma (n = 5,774 [7.8%])	Adjusted† OR (95% CI), asthma (n = 4,941 [8.0%])	Crude OR (95% CI), asthma (n = 10,238 [13.7%])	Adjusted‡ OR (95% CI), asthma (n = 7,585 [12.0%])
Pregnancy characteristic						
Preeclampsia or eclampsia	272 (4.7)	549 (5.4)	1.23 (1.08 to 1.40)	1.10 (0.95 to 1.27)	1.27 (1.15 to 1.39)	1.17 (1.05 to 1.31)
Placental abruption	27 (0.5)	39 (0.4)	1.07 (0.72 to 1.59)	1.20 (0.79 to 1.83)	1.27 (0.90 to 1.78)	1.10 (0.71 to 1.72)
Labor characteristic						
Mode of delivery						
Vaginal noninstrumental delivery	4,297 (74.4)	7,520 (73.5)	Reference	Reference	Reference	Reference
Elective CS (before start of labor)	338 (5.9)	855 (8.4)	1.26 (1.12 to 1.42)	1.28 (1.12 to 1.45)	1.33 (1.24 to 1.44)	1.32 (1.20 to 1.44)
Vaginal instrumental delivery	407 (7.0)	679 (6.6)	1.02 (0.92 to 1.14)	1.05 (0.93 to 1.17)	1.12 (1.03 to 1.22)	1.14 (1.03 to 1.25)
Emergency CS before or after start of labor	539 (9.3)	1,160 (11.3)	1.18 (1.08 to 1.30)	1.16 (1.05 to 1.29)	1.32 (1.24 to 1.41)	1.23 (1.14 to 1.34)
Missing	193 (3.3)	24 (0.2)				
Birth outcome and postpartum						
Birth weight (g)						
Mean	3,592	3,539	−0 (−16 to 15)	−11 (−27 to 6)	−29 (−41 to −17)‡	−43 (−57 to −30)‡
Missing	303 (0.4)	162 (0.2)				
Gestational age (wk)						
Mean	39.4	39.3	−0.03 (−0.09 to 0.02)	−0.04 (−0.10 to 0.01)	−0.11 (−0.15 to −0.07)‡	−0.10 (−0.14 to −0.05)‡
Missing	76 (0.1)	14 (0.0)				
Small for gestational age						
Yes	121 (2.1)	216 (2.1)	0.97 (0.80 to 1.16)	0.95 (0.77 to 1.16)	1.07 (0.93 to 1.24)	1.12 (0.94 to 1.33)
Missing	23 (0.4)	20 (0.2)				
Large for gestational age						
Yes	272 (4.7)	393 (3.8)	1.15 (1.01 to 1.30)	1.03 (0.89 to 1.19)	1.01 (0.91 to 1.13)	0.87 (0.76 to 0.99)
Missing	23 (0.4)	20 (0.2)				

BMI, Body mass index; CS, cesarean section.

*Asthma recorded in the Swedish Medical Birth Register, asthma diagnosis in the Swedish National Patient Register, and/or asthma medication dispensed at least twice according to the Swedish Prescribed Drug Register.

†Adjusted for age, BMI, parity, smoking at antenatal care admission, country of birth, cohabitation/marital status, and level of education.

‡ $P < .001$.

TABLE E3. The association between asthma and perinatal characteristics: Adjusted logistic and linear regression cohort, cousin and sibling analyses*

			Adjusted [‡] OR (95% CI)					
	Previous asthma (n[%])	Current asthma (n[%])	Previous all population logistic/linear regression	Current all population logistic/linear regression	Previous cousins conditional logistic/linear regression	Current cousins conditional logistic/linear regression	Previous sisters conditional logistic/linear regression	Current sisters conditional logistic/linear regression
Characteristic								
Pregnancy characteristic								
Preeclampsia or eclampsia	2,835 (5.1)	1,145 (5.6)	1.07 (1.03 to 1.12)	1.29 (1.23 to 1.35)	1.10 (0.99 to 1.21)	1.19 (1.06 to 1.32)	1.06 (0.91 to 1.21)	1.37 (1.15 to 1.58)
Placental abruption	239 (0.4)	113 (0.6)	1.25 (1.10 to 1.42)	1.26 (1.08 to 1.48)	1.13 (0.80 to 1.47)	1.19 (0.77 to 1.61)	1.01 (0.59 to 1.43)	1.19 (0.59 to 1.79)
Labor characteristic								
Mode of delivery								
Vaginal noninstrumental delivery	40,555 (73.0)	14,676 (71.6)	Reference	Reference	Reference	Reference	Reference	Reference
Elective CS (before start of labor)	4,231 (7.6)	1,779 (8.7)	1.16 (1.12 to 1.21)	1.50 (1.44 to 1.56)	1.11 (1.02 to 1.21)	1.63 (1.44 to 1.81)	1.04 (0.89 to 1.19)	1.45 (1.20 to 1.69)
Vaginal instrumental delivery	4,356 (7.8)	1,477 (7.2)	1.05 (1.01 to 1.08)	1.16 (1.12 to 1.21)	1.05 (0.97 to 1.12)	1.21 (1.09 to 1.32)	1.05 (0.93 to 1.17)	1.20 (1.03 to 1.38)
Emergency CS before or after start of labor	6,097 (11.0)	2,444 (11.9)	1.15 (1.11 to 1.18)	1.36 (1.31 to 1.41)	1.19 (1.10 to 1.27)	1.16 (0.87 to 1.44)	1.07 (0.96 to 1.18)	1.34 (1.16 to 1.52)
Missing	317 (0.6)	133 (0.6)						
Birth outcome and postpartum								
Birth weight (g)								
Mean	3,540	3,503	−36 (−41 to −30) [‡]	−64 (−73 to −55) [‡]	−18 (−27 to −8) [‡]	−59 (−72 to −47) [‡]	−7 (−17 to 4)	−61 (−75 to −48) [‡]
Missing	87 (0.2)	43 (0.2)						
Gestational age (wk)								
Mean	39.3	39.2	−0.06 (−0.08 to −0.05) [‡]	−0.19 (−0.22 to −0.16) [‡]	−0.07 (−0.10 to −0.03) [‡]	−0.11 (−0.15 to −0.06) [‡]	−0.02 (−0.06 to 0.01)	−0.08 (−0.12 to −0.04) [‡]
Missing	9 (0.0)	4 (0.0)						
Small for gestational age								
Yes	1,302 (2.3)	538 (2.6)	1.01 (0.95 to 1.07)	1.43 (1.34 to 1.52)	1.04 (0.90 to 1.18)	1.32 (1.11 to 1.52)	0.90 (0.75 to 1.05)	1.46 (1.17 to 1.76)
Missing	98 (0.2)	48 (0.2)						

(continued)

TABLE E3. (Continued)

Characteristic	Previous asthma (n[%])	Current asthma (n[%])	Adjusted† OR (95% CI)					
			Previous all population logistic/linear regression	Current all population logistic/linear regression	Previous cousins conditional logistic/linear regression	Current cousins conditional logistic/linear regression	Previous sisters conditional logistic/linear regression	Current sisters conditional logistic/linear regression
Large for gestational age								
Yes	2,064 (3.7)	819 (4.0)	0.98 (0.93 to 1.02)	0.84 (0.79 to 0.89)	0.94 (0.84 to 1.04)	0.83 (0.74 to 0.92)	1.00 (0.84 to 1.15)	0.82 (0.68 to 0.96)
Missing	98 (0.2)	48 (0.2)						

BMI, Body mass index; CS, cesarean section.

*Exposure is Previous asthma from the year before pregnancy or earlier and Current asthma in the year before or during pregnancy.

†Adjusted for age, BMI, parity, smoking at antenatal care admission, country of birth, cohabitation/marital status, and level of education.

‡*P* < .001.

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